ONLINE METHODS

Research Subjects

The descriptions of the individual cohorts are presented as a **Supplementary Note**. The discovery set for the meta-analysis consisted of 14 studies with body mass index (BMI) measured in childhood (age range 2-18 years, except for ALSPAC, which also leveraged BMI data available from the first four clinical examinations prior to 2 years old) and genome-wide genotype data available by the beginning of May 2010): the Avon Longitudinal Study of Parents and Children (ALSPAC, n= 976 cases / 1,244 controls); Northern Finland 1966 Birth Cohort (NFBC1966, n= 700 cases / 521 controls); British 1958 Birth Cohort – Type 1 Diabetes Genetics Consortium subset (B58C-T1DGC, n= 192 cases / 367 controls); British 1958 Birth Cohort – Wellcome Trust Case Control Consortium Subset (B58C-WTCCC, n= 188 cases / 428 controls); French Young study (FRENCH YOUNG, 670 cases/ 349 controls); Lifestyle Immune System Allergy Study (LISA, n=27 cases / 250 controls); Western Australian Pregnancy Cohort study (RAINE, n= 232 cases / 125 controls); Children's Hospital of Philadelphia (CHOP, n= 1,445 cases / 2,802 controls); Essen Obesity Study (ESSEN, n=397 cases / 435 controls); Helsinki Birth Cohort Study (HBCS, n= 261 cases/ 403 controls); Cardiovascular Risk in Young Finns Study (YF, n= 167 cases / 537 controls); Copenhagen Study on Asthma in Childhood (COPSAC, n= 62 cases / 99 controls); CM-GOYA study (CM-GOYA; n= 21 cases / 34 controls) and Generation R Study (GENERATIONR, n= 192 cases / 724 controls).

The phenotypically comparable cohorts used for the replication effort were Healthy Lifestyle in Europe by Nutrition in Adolescence study (HELENA; n= 56 cases / 563 controls), Young Hearts studies (n= 44 cases / 450 controls), the Lifestyle – Immune System – Allergy Study plus German Infant Study on the influence of Nutrition Intervention (LISA+GINI, n= 40 cases / 457 controls), Children's Health Study (CHS; n= 311 cases / 330 controls), Avon Longitudinal Study of Parents and Children (ALSPAC; n= 1,452 cases / 1,042 controls), INfancia y Medio Ambiente [Environment and Childhood] Project (INMA; n= 55

cases / 213 controls), Project Viva (VIVA; n= 48 cases / 184 controls), Prevention and incidence of asthma and mite allergy birth cohort study (PIAMA; n= 68 cases / 85 controls) and the Northern Finland 1986 Birth Cohort (NFBC1986; n= 744 cases / 759 controls). The two extreme obesity replication cohorts consisted of 705 German trios and SCOOP-UK cohort (n= 1,509 cases / 2,674 controls). Selected signals were further investigated in the GIANT[1] cohort, using the publically available dataset at http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files.

All cases and controls were of European ancestry. Cases were defined as having a BMI>95th percentile at any point in childhood. Controls were defined as consistently having a BMI<50th percentile throughout childhood for all measurements available for that individual. BMI percentiles were based on national standard growth curves, except in the Helsinki Birth Cohort Study (HBCS) and the Northern Finland 1966 Birth Cohort (NFBC1966) as pediatric measurements were made two decades ago, thus contemporary curves will not be appropriate. HBCS and NFBC1966 generated their own reference curves. In addition, the density of data available longitudinally in the ALSPAC study gave rise to two differences in cases/control definition. Firstly, this collection factored in subjects from the first four clinical examinations of childhood and thus participants less than 2 years old in their consideration of trait definition (sensitivity analyses considering the use of data from participants limited to being over the age of 2 years old are included in **Supplementary Tables 7-9**). Secondly, owing to the regularity of measures (11 measures available), controls in the ALSPAC sample were defined as those BMI<50th percentile on at least 5 occasions. Known syndromic cases of obesity were excluded, since these individuals are likely to have a different underlying genetic architecture. Unless otherwise noted, all discovery sample analysis followed the same protocol and analysis plan.

Informed consent was obtained from all discovery study participants (or parental consent, as appropriate), and study protocols were approved by the local ethics committees.

Statistical approaches

Stage 1: GWA meta-analysis of childhood obesity

Statistical analysis within discovery samples

Genotypes were obtained using high-density SNP arrays, and then imputed for ~2.54 million HapMap CEU SNPs (Phase II, release 22, http://hapmap.ncbi.nlm.nih.gov). Prior to imputation, we excluded SNPs with a Hardy-Weinberg equilibrium *P*-value (HWEP) < 1.0×10^{-6}, call rate < 95 percent and minor allele frequency < 1 percent. Post imputation, SNPs imputed with IMPUTE were excluded if the proper info was < 0.40 and SNPs imputed with MACH were excluded if the r2hat was < 0.30. SNPs were also excluded post imputation if the minor allele frequency was < 1 percent. The association between each SNP and case-control status was assessed in each study sample using logistic regression of case-control against genotype, assuming an additive model and taking into account genotype uncertainty. Imputed genotypes were only used where directly-assayed genotypes were unavailable. Unless otherwise stated, all discovery analysis followed the former protocol.

Meta-analysis of discovery samples

Prior to meta-analysis, SNPs with a minor allele frequency <1% and poorly-imputed SNPs (proper_info ≤0.4 [SNPTEST]; r^2 ≤0.3 [MACH2QTL]) were filtered. Fixed effects meta-analyses were conducted by two independent investigators (J.B., H.R.T.). Meta-analysis was performed using the software package: METAL (http://www.sph.umich.edu/csg/abecasis/metal/index.html); Genomic control[15] was applied to each cohort prior to meta-analysis. Meta-analysis was carried out using the inverse-variance method, fixed effects model was assumed. SNPs available for less than half of the total expected sample were excluded. We used the Cochran Q test to assess evidence of between-study heterogeneity of effect sizes.

A total of 2.7 million SNPs were analyzed in the meta-analysis unfiltered for the number of cohorts they appear in. Seven SNPs reached genome wide significance, all of which were reported previously in the adult BMI GWAS[1,16]. Those loci that reached a *P*-value threshold of $<5x10^{-6}$ in the discovery meta-analysis, and were not identified with obesity related traits before (n = 8), were considered for further follow-up in additional samples.

Stage 2: Follow-up of three lead signals in additional samples

Follow-up samples, genotyping and analysis

We used nine study samples representing a comparable dataset (combined n = 2,818 cases and 4,083 controls) and two study samples representing an extreme obesity dataset (combined n = 2,214 cases and 2,674 controls) to follow up the eight novel signals from the GWAS discovery meta-analysis (represented by index SNPs: rs2300095, rs4833407, rs4864201, rs28636, rs1290002, rs9568856, rs9299 and rs17697518). If the index SNP was unavailable, the most closely correlated proxy available was substituted. In four of the replication studies, the index SNPs were imputed from genome-wide genotype data.

Meta-analyses

We performed fixed effects inverse variance meta-analyses of the association results for the eight lead signals in the fourteen discovery samples and the nine comparable replication samples. We subsequently did the same with the fourteen discovery samples combined with the two extreme cohorts. Lastly we combined all datasets for the final overall meta-analysis. Fixed effects meta-analyses were conducted independently by two investigators (J.B, H.R.T.), again using METAL.

15. Devlin, B. & Roeder, K. Genomic control for association studies. *Biometrics* **55**, 997-1004 (1999).

16. Willer, C.J. et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* **41**, 25-34 (2009).